Scientific paper

CO_2 Improved Synthesis of Benzimidazole with the Catalysis of a New Calcium 4-Amino-3-hydroxybenzoate

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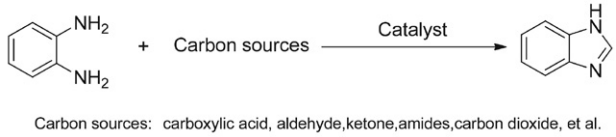
Abstract

In this paper, we explored the synthesis of benzimidazole by the reaction of DMF and *o*-phenylenediamine. In the process of catalyst screening, we found that 4-amino-3-hydroxybenzoic acid, benzoic acid, and benzene-1,3,5-tricarboxylic acid could catalyze the reaction. Moreover, the calcium 4-amino-3-hydroxybenzoate and CO_2 could more effectively catalyze the reaction, the synergistic effect of CO_2 and 4-amino-3-hydroxybenzoic acid calcium salt can increase the yield of benzimidazole from 28% to 94%.

Keywords: Calcium 4-amino-3-hydroxybenzoate, CO_2, benzimidazole, weak acid catalysis

1. Introduction

Benzimidazole and its derivatives are fundamental building blocks in many kinds of functional compounds, especially in drugs and bioactive molecules,[1–4] and widely used in anti-cancer,[5] anti-inflammatory,[6] anti-bacterial,[7] anti-oxidant,[8] anti-coagulant[9] and so on.[10] Therefore, it is of great significance to find a simple, economic and environmentally friendly method for the synthesis of benzimidazoles. Up to now, cycloaddition reaction of *o*-phenylenediamine and carbon source molecule seems to be an effective method for the synthesis of benzimidazoles. The carbon source generally involves a carboxylic acid,[9,11] aldehyde,[1,3,10] ketone,[12] amide,[11,13,14] and carbon dioxide[2,15,16] (Scheme 1). As a special amide, *N*,*N*-dimethylformamide (DMF) is not only a carbon source but also an effective polar solvent for the synthesis of benzimidazoles.[11,14,15,17,18]



Scheme 1. Carbon sources in the synthesis of benzimidazoles with *o*-phenylenediamine.

Catalysts, such as inorganic acids,[19] organic acids,[10] alkalis,[18] Lewis acids,[20] transition metals salts,[21] organometallic complexes,[22] play an important role in the synthesis of benzimidazoles. Hydrochloric acid is usually used in the synthesis of benzimidazoles, but it is corrosive and impossible to be reused.[19] Then many catalysts had been prepared for this reaction, for instance, azole-anion-based aprotic ionic liquids with tetrabutylphosphonium hydroxide,[23] ionic liquids of hydrochloric acid,[24] glyoxylic acid,[10] $B(C_6F_5)_3$[16] and zinc acetate dehydrate.[11] But they are usually used in combination with reducing substances such as hydrosilane, hydrogen, boron phosphorus and transition metal salts. In short, their application is undesirable under the green chemistry principles. It is of paramount importance to find an effective and pollution-free catalyst for the synthesis of benzimidazoles.

Recently, Ru,[25] Mn,[26] Co,[27,32] Cu,[28] Zr,[29] Fe[30] and Ir[31] organometallic complexes have been used to catalyze the synthesis of benzimidazoles, and the recycle times of catalysts were increased obviously. That provided a new idea for designing catalysts to catalyze the synthesis of benzimidazoles. When we investigated the catalytic mechanism of these organometallic salts, it was found that the main catalytic species was still hydrogen cation (*i.e.* proton).[15,24] Hence, we planned to consider catalytic effects of several acids or salts especially 4-amino-3-hydroxybenzoic acid

and its calcium salt on the synthesis of the benzimidazole and the results obtained are described in this paper.

2. Experimental

2. 1. Chemicals

All of the reagents were purchased from commercial sources and used without further purification. Benzene-1,3,5-tricarboxylic acid, 4-amino-3-hydroxybenzoic acid, *o*-aminophenol, calcium benzoate, *N*,*N*-dimethylformamide and *o*-phenylenediamine were purchased from Shanghai Aladdin Biological Technology Co., Ltd. (Shanghai, China). $Ca(NO_3)_2{\cdot}4H_2O$, phenol and benzoic acid were purchased from Sinopharm Chemical Regagent Co., Ltd. (Shanghai, China). Calcium benzene-1,3,5-tricarboxylate was synthesized according to the method in the literature.[32]

2. 2. Apparatus

FT-IR spectra were measured on a Perkin–Elmer FT-IR spectrum. Fluorescence spectra were obtained by an Agilent Technologies Cary Fluorescence Spectrophotometer analyzer. NMR spectra in DMSO-d_6 were recorded with an Agilent 500 MHz DD2 spectrometer. The molecular structure of calcium 4-amino-3-hydroxybenzoate was obtained on a Bruker D8 VENTURE diffractometer. X-ray powder diffraction (XRD) spectra were recorded on a Rigaku (SmartLab 9KW) diffractometer for a Cu-target tube.

2. 3. Preparation of Calcium 4-Amino-3-hydroxybenzoate

4-Amino-3-hydroxybenzoic acid (91.8 mg, 0.6 mmol) and $Ca(NO_3)_2$ $4H_2O$ (141.7 mg, 0.6 mmol) were dissolved in MeOH (15 mL) in a flask, then the reaction mixture was stirred and refluxed for 3 hours. The resulting solution was cooled to room temperature and filtered. The filtrate was allowed to stand at room temperature for slow evaporation. IR: 3377.96 (m, γ_{O-H}), 3307.00 (m, γ_{N-H}), 1609.45 (m, δ_{N-H}), 1532.81 (vs, γ_{as} COO), 1413.58 (vs, γ_{as} COO), 1223.39 (s, δ_{C-O}), 1024.68 (m, γ_{C-N}).

2. 4. Structure Determination

Single-crystal X-ray diffraction measurements were carried out on a Bruker D8 VENTURE diffractometer. The diffraction data were collected with MoKα radiation (λ = 0.71073 Å). The structures were solved by direct methods and refined against F^2 by full-matrix least-squares methods with SHELXTL-2014.[33] All non-hydrogen atoms were refined with anisotropic thermal parameters. The hydrogen atoms were set in calculated positions and refined as riding atoms with a common fixed isotropic thermal parameter. Crystal data and details of the data collection and the structure refinements are given in Table S1.

2. 5. The Synthesis of Benzimidazole

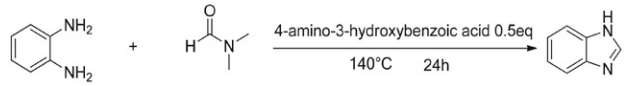
o-Phenylenediamine (108.1 mg, 1 mmol) was catalyzed by calcium 4-amino-3-hydroxybenzoate (0.25 eq) with CO_2 (3 bar) and DMF (2 mL) in a high-pressure reactor. Most of the *o*-phenylenediamine was consumed completely after the reaction mixture was stirred at 140 °C for 24 h. Then the reaction mixture was extracted with ethyl acetate, and the crude product (110.8 mg, 94%) was purified by column chromatography through a silica-gel column to afford the desired products eluted by CH_3OH and CH_2Cl_2. Anal. Calcd. (%) for $C_7H_4N_2$: C, 71.10; H, 5.12; N, 23.71. Found (%): C, 70.76; H, 5.51; N, 23.29. ^{1}H NMR (500 MHz, DMSO-d_6, 25 °C, TMS) δ 12.43 (s, 1H), 8.20 (s, 1H), 7.62–7.55 (m, 2H), 7.19 (dt, J_1 = 6.0 Hz, J_2 = 3.4 Hz, 2H). ^{13}C NMR (500 MHz, DMSO-d_6, 25 °C, TMS): δ 141.78, 121.56. IR: 3064.18 (m, γ_{C-H}), 1592.49 (s, γ_{C-N}), 1555.05 (w, γ_{C-N}), 1480.17 (s, γ_{C-N}), 1203.69 (m, γ_{C-H}), 742.89 (m, δ_{N-H}). ESI-MS (CH_3OH, *m/z*): 119.05 (M^+). UV-Vis (CH_3OH): 243, 278.

3. Results and Discussion

Initially, the 4-amino-3-hydroxybenzoic acid-catalyzed cycloaddition reaction of *o*-phenylenediamine and DMF was investigated. The equivalents of the catalyst used, reaction temperatures and yields are listed in Table 1.

As shown in Table 1, the reaction temperature (Table 1, entries 1–5) and the equivalent of 4-amino-3-hydroxybenzoic acid used (Table 1, entries 5–9) could significantly influnce the reaction yield. The benzimidazole could be obtained in 84% yield after 24 hours of reaction at 140 °C when the equivalent of 4-amino-3-hydroxybenzoic acid was 0.5 (Table 1, entry 5).

Table 1. The cyclization of *o*-phenylenediamine and DMF catalyzed by 4-amino-3-hydroxybenzoic acid

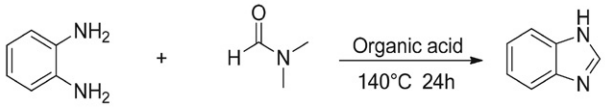


Entry	Cats [equiv.]	*T* [°C]	Yield [%]
1	0.5	100	26
2	0.5	110	40
3	0.5	120	57
4	0.5	130	71
5	0.5	140	84
6	0.25	140	67
7	0.125	140	37
8	0.05	140	15
9	0	140	–

reaction condition: *o*-phenylenediamine (1 mmol), DMF (2 mL), reaction time 24 h, isolated yield

With the optimized reaction conditions, the catalytic performance of different weak organic acids was investigated (Table 2).

Table 2. The cyclization of *o*-phenylenediamine and DMF catalyzed by an organic acid



Entry	Catalyst	Cats [equiv.]	Yield [%]
1	phenol	0.5	trace
2	*o*-aminophenol	0.5	trace
3	benzoic acid	0.5	85
4	4-amino-3-hydroxybenzoic acid	0.5	84
5	benzene-1,3,5-tricarboxylic acid	0.167	95

reaction condition: *o*-phenylenediamine (1 mmol), DMF (2 mL), 24 h at 140 °C, isolated yield

As shown in Table 2, the yield of benzimidazole increased with the increasing of acidity of the catalyst. The phenol (pK_a ≈ 9.99) and *o*-aminophenol (pK_a ≈ 9.28) could not effectively catalyze the synthesis of benzimidazole. The benzoic acid (pK_a ≈ 4.20), benzene-1,3,5-tricarboxylic acid (pK_a ≈ 2.12) and 4-amino-3-hydroxybenzoic acid (pK_a ≈ 4.74) could effectively catalyze the synthesis of benzimidazole.[34] It is further proved that the catalytic species is proton.[15,24] But when the reactions (presented in Tables 1 and 2) were performed, it was difficult to perform effective separation and recovery of the catalyst. Therefore, instead of the acids metal salts were used to catalyze this reaction.

First, calcium 4-amino-3-hydroxybenzoate was prepared, its single crystal structure was determined by X-ray crystallography at 0 °C, showing that it crystallized in the monoclinic space group *C*2/*c* and showed an irregular dodecahedron. The molecular structure and coordination polyhedron of calcium 4-amino-3-hydroxybenzoate are shown in Figure 1. The calcium is in the center of eight oxygen atoms, four of them are from two polycarboxylic

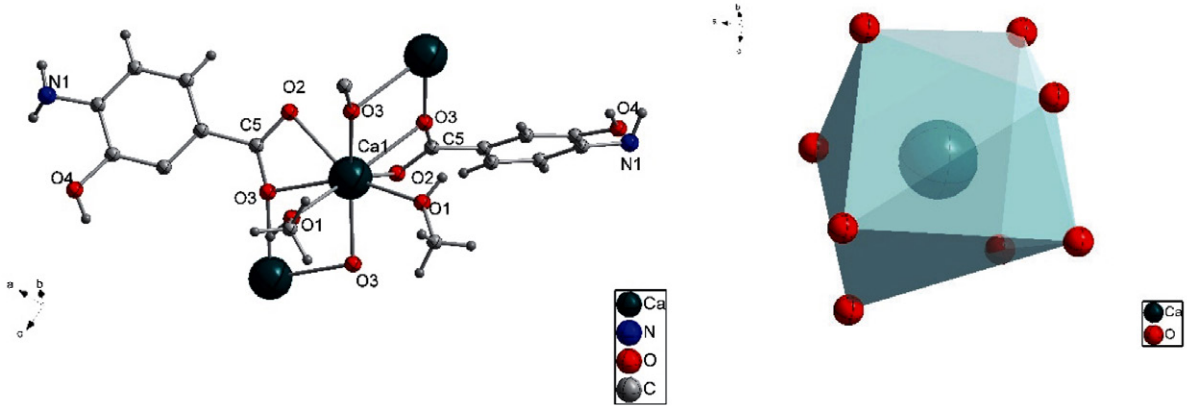


Figure 1. The molecular structure (left) and coordination polyhedron (right) of calcium 4-amino-3-hydroxybenzoate.

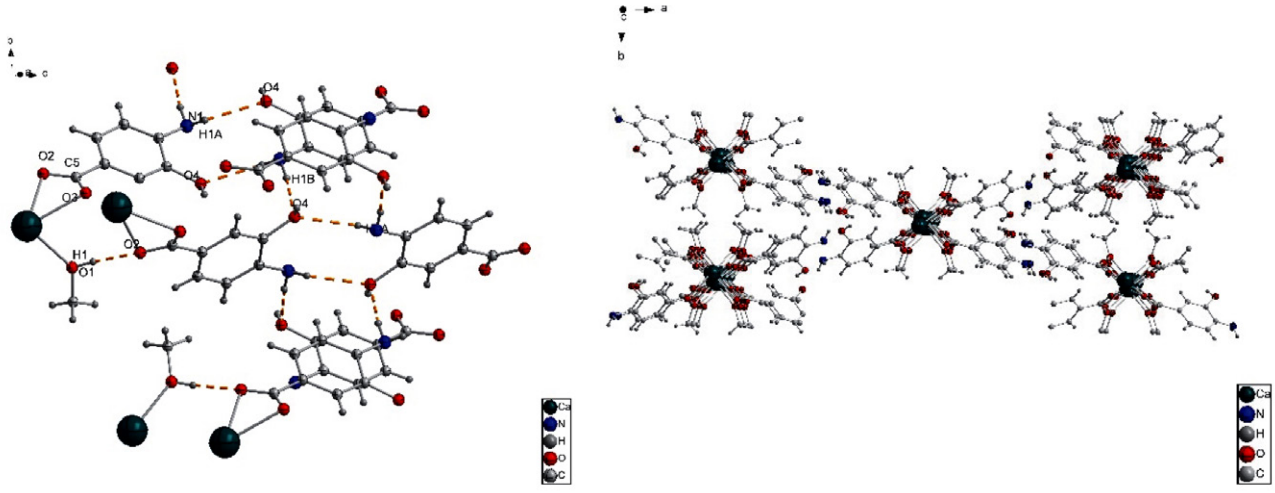


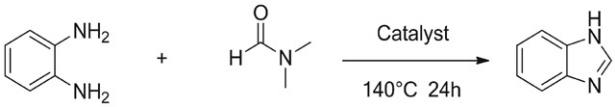
Figure 2. Structure of the calcium 4-amino-3-hydroxybenzoate showing the hydrogen bonding interactions (left) and packing diagram (right).

groups, two of them are from CH_3OH, and two of them are from two polycarboxylic groups coordinated with other calcium atoms. The bond length of Ca–O is in the range of 2.384–2.517 Å, and there is a little difference in the distance between calcium atoms and eight oxygen atoms. The result of crystal structure analysis is consistent with the FT-IR spectrum (Figure S3).

There are two kinds of hydrogen bonds in the structure of calcium 4-amino-3-hydroxybenzoate, shown in Figure 2 and Table S3. O(1)–H(1)···O(2) formed between the hydrogen atom on the methanol hydroxyl group coordinated with calcium ion and the oxygen atom on the carboxylic acid coordinated with the adjacent calcium ion. The distance between H(1) and acceptor O(2) was 1.92 Å, and the angle between donor and acceptor was 176°. The other more weak interaction N(1)–H(1B)···O(4) formed between the hydrogen atom on the ligand amino group and the oxygen atom on the hydroxyl group of the adjacent ligand. The distance between H(1B) and acceptor O(4) was 1.98 Å, and the angle between donor and acceptor was 167°. Moreover, the structure of the calcium 4-amino-3-hydroxybenzoate had some porous framework features, due to many uncoordinated amino and hydroxyl groups.

The catalytic performance of the calcium 4-amino-3-hydroxybenzoate was tested, and compared with that of calcium benzoate, calcium benzene-1,3,5-tricarboxylate and 4-amino-3-hydroxybenzoic acid (Table 3.).

Table 3. The cyclization of *o*-phenylenediamine and DMF catalyzed by various calcium salts and 4-amino-3-hydroxybenzoic acid



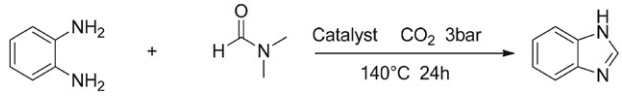
Entry	Catalyst	Cats [equiv.]	Yield [%]
1	calcium benzoate	0.5	10
2	calcium benzene-1,3,5-tricarboxylate	0.167	20
3	calcium 4-amino-3-hydroxybenzoate	0.25	28
4	4-amino-3-hydroxybenzoic acid	0.5	84

reaction condition: *o*-phenylenediamine (1 mmol), DMF (2 mL), 24 h, 140 °C, isolated yield

As shown in Table 3, although the catalyst separation became easier, the calcium salts (*i.e.* calcium benzoate, calcium benzene-1,3,5-tricarboxylate and calcium 4-amino-3-hydroxybenzoate) did not exhibit the desired catalytic activity. Especially, with comparing corresponding carboxylic acid, the three calcium salts of thecarboxylic acids lost their catalytic activity seriously. Through exploration of their molecular structures, it was found that the benzoic acid exists in the crystal cell structure of calcium benzoate (Figure S5). And one of carboxyl groups of benzene-1,3,5-tricarboxylic acid was monodentate and might provide an active hydrogen (Figure S6). In the structure of calcium 4-amino-3-hydroxybenzoate, the active hydrogen might originate from an un-coordinated hydroxyl group. This small amount of the hydrogen in the crystal cell might be the catalytic species.

In order to study the catalysis of weak acids further, CO_2 was introduced into the reaction system of the cyclization of *o*-phenylenediamine and DMF. When we introduced CO_2 at 3 bar into the reaction system (and no catalyst was added), nearly no benzimidazole was obtained (Table 4, entry 1). When the reaction was repeated with the addition of 0.5 equivalent of 4-amino-3-hydroxybenzoic acid, the yield of benzimidazole increased to 93% (Table 4, entry 2), which was higher than the previously obtained 84% (Table 3, entry 4). It was comfirmed that the presence of CO_2 improved the reaction yield. Hence we introduced CO_2 into other catalytic reaction systems of the cyclization of *o*-phenylenediamine and DMF (Table 4, entries 3–5). In calcium benzoate and calcium benzene-1,3,5-tricarboxylate catalytic reaction systems, no obvious improvement effect occurred (Table 4, entries 3 and 4). But in calcium 4-amino-3-hydroxybenzoate catalytic reaction system, the yield of benzimidazole (Table 4, entry 5) was almost the same as that of 4-amino-3-hydroxybenzoic acid catalytic reaction system. CO_2 significantly improved the catalytic activity of calcium 4-amino-3-hydroxybenzoate. However, when the reaction mixture with separated calcium 4-amino-3-hydroxybenzoate catalyst was repeated, it lost its activity (Table 4, entry 6). By comparing the XRD patterns before and after its use (Figure 3), it was found that the structure of calcium 4-amino-3-hydroxybenzoate was destroyed during the reaction and can thus not be used again.

Table 4. The cyclization of *o*-phenylenediamine and DMF catalyzed by the calcium salts in the presence of CO_2



Entry	Catalyst	Cats [equiv.]	Yield [%]
1	no	0	trace
2	4-amino-3-hydroxybenzoic acid	0.5	93
3	calcium benzoate	0.5	12
4	calcium benzene-1,3,5-tricarboxyate	0.167	23
5	calcium 4-amino-3-hydroxybenzoate	0.25	94
6	calcium 4-amino-3-hydroxybenzoate, reused	0.25	32

reaction condition: *o*-phenylenediamine (1 mmol), DMF (2 mL), 24 h, 140 °C, 3 bar CO_2, isolated yield

Although, the calcium 4-amino-3-hydroxybenzoate could not be reused, CO_2 also could significantly improved

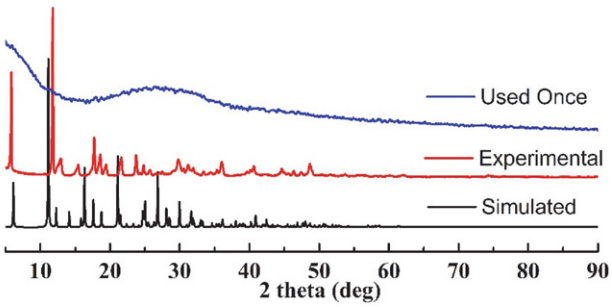
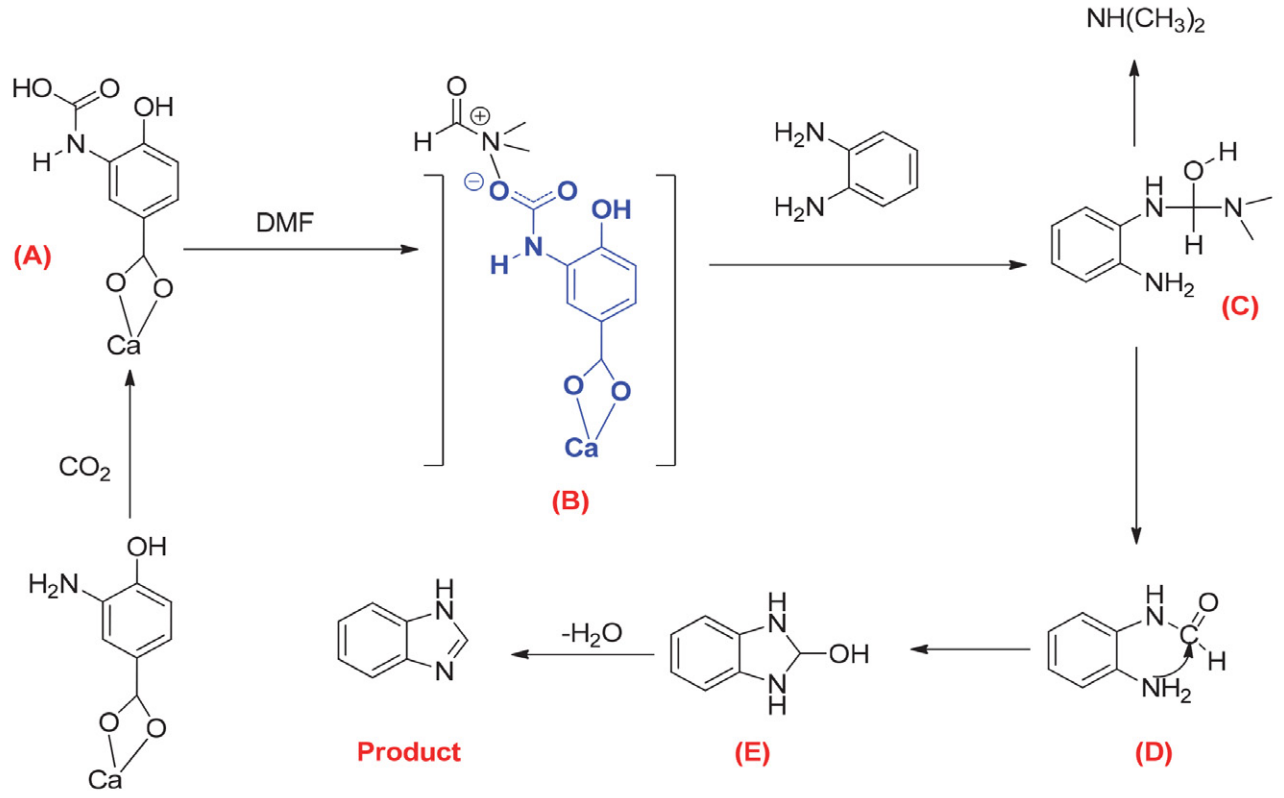


Figure 3. XRD pattern of the simulated and experimental calcium 4-amino-3-hydroxybenzoate and the catalyst used once.

catalytic activity of calcium 4-amino-3-hydroxybenzoate whithout improved catalytic activity of the calcium benzoate and calcium benzene-1,3,5-tricarboxylate. That was still an interesting problem.

4-amino-3-hydroxybenzoate has the above group characteristics. On the basis of the experimental results and previous reports,[14,20,24] a possible mechanism of carbon dioxide-assisted catalytic reaction was proposed (Scheme 2). First, the CO_2 reacted with the un-coordinated amine of calcium 4-amino-3-hydroxybenzoate to form an intermediate A. Then the intermediate A activated DMF to form an intermediate B. The activated DMF reacted with the *o*-phenylenediamine to form an intermediate C, and the rest of the intermediate B returned to the intermediate A and participated in the further activation of DMF. The intermediate C lost a dimethylamine to form an intermediate D. Finally, the intermediate D fromed the product through the intermediate E. Because the intermediate A could not return to the original calcium 4-amino-3-hydroxybenzoate. Hence, the XRD pattern of the used catalyst was no longer the original pattern of calcium 4-amino-3-hydroxybenzoate.



Scheme 2. Possible reaction mechanism.

Why CO_2 could significantly improve catalytic activity of calcium 4-amino-3-hydroxybenzoate? According to the literature, CO_2 easily interacts with amino groups forming carbamate,[35] and many porous MOF materials with amino groups can adsorb CO_2.[36–38] In addition, more studies showed that a mixture of an alcohol and an amine was a good material for CO_2 capture and enrichment.[39,40] The un-coordinated amino and hydroxyl of calcium

4. Conclusions

In this paper, the catalytic performance on the synthesis of the benzimidazole was compared. The catalysts investigated were phenol, *o*-aminophenol, benzoic acid, 4-amino-3-hydroxybenzoic acid and benzene-1,3,5-tricarboxylic acid. We further verified that the proton was the key factor in the catalysis of this reaction. In order to improve the reusability of the catalyst, the catalytic perfor-

mance of calcium benzoate, calcium benzene-1,3,5-tricarboxylate and calcium 4-amino-3-hydroxybenzoate were evaluated, but they did not provide the desired results. When CO_2 was added as weak acid to catalyze this reaction, the yield was very unsatisfactory. But an interesting result was obtained showing that CO_2 could significantly improve the catalytic activity in the presence of calcium 4-amino-3-hydroxybenzoate. The cooperation of carbon dioxide and this salt increased the yield of product from 28% to 94%, and a possible mechanism was proposed to explain why cooperation of carbon dioxide and the salt could improved the catalytic activity.

Acknowledgements

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Supplementary Material

Supplementary (synthesis of the benzimidazole, IR, ^1H and ^{13}C NMR, UV-Vis) data associated with this article can be found, in the online version. Crystallographic data for structures reported in this paper in the form of CIF files have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication CCDC No.2011696. Copy of the data can be obtained free of charge from the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: +44-1223-336033; E-mail: deposit@ccdc.cam,ac.uk).

5. References

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Povzetek

V tem prispevku predstavljamo raziskavo sinteze benzimidazola z reakcijo DMF in *orto*-fenilendiamina. Med preučevanjem učinkovitosti različnih možnosti smo ugotovili, da so 4-amino-3-hidroksibenzojska kislina, benzojska kislina in benzen-1,3,5-trikarboksilna kislina uspešni katalizatorji za to reakcijo. Kalcijev 4-amino-3-hidroksibenzoat se je v prisotnosti CO_2 izkazal kot še posebej učinkovita možnost, saj se je zaradi sinergističnega učinka med CO_2 in kalcijevo soljo 4-amino-3-hidroksibenzojske kisline izkoristek benzimidazola povečal z 28 % na 94 %.